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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/614,282	LEE ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *36-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/18/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

This Application was filed July 8, 2003 and claims priority to US application 60/494,270, filed July 9, 2002.

Claims 1-39 are under consideration.

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-16, 20-35) in the reply filed on October 18, 2004 is acknowledged. The traversal is on the ground(s) that the search for Group I would encompass a search for the subject matters of Groups II and III and that any additional search would not impose a serious burden upon the Examiner. The argument has been considered. The Examiner will examine the claims of Groups I and II (claims 1-35) as the claims are drawn to *in vitro* methods of making the plasmid and expressing a nucleic acid product with at least two cistrons. However, the argument regarding including Group III in the examination is not found persuasive because the search and analysis of art using nucleic acids to treat a patient involves *in vivo* methods are materially and methodically different from an *in vitro* study. The requirement is still deemed proper and is therefore made FINAL.

Claims 36-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group III, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on October 18, 2004. Claims 1-35 are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for constructs pAcGalLuc, pAcGal*EMCV*Luc, pAcGal*Antp*Luc, pAcGal*Lab*Luc, pAcDsRedEGFP, pAcDsRed*LabEGFP,* pCycBGalLuc, pCycBGal*EMCV*Luc, pCycBGal*Lab*Luc, pAcGal*Ubx*Luc,pGal*N*Luc, pCMVGalLuc, pCMVGal*EMCV*Luc, pCMVGal*hBip*Luc, pCMVGal*A1*Luc, pAcLab(1-239), pAcLab(1-215), pAcLab(45-239), pAcLab(45-215), pAcLab(1-74_187-215), pAcLab(1-74_187-239), pAcLab(124-7 GGGG), A1(136-9AAAA), pAcEGFP*Lab*Hyg, pOpIE2GalLuc, pOpIE2Gal*EMCV*Luc,pOpIE2Gal*lab*Luc, and pOpIE2GalΔ*lab*Luc, pPolhLuc*EMCV*EGFP, pPolhLuc*lab*EGFP, and pPolhLuc*EMCV*GFP does not reasonably provide enablement for broad claims to a nucleic acid vector for the expression of at least two cistrons comprising any promoter, a variant, fragment, homolog of SEQ ID NO.1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention consists of nucleic acid vectors (pAcGalLuc, pAcGal*EMCV*Luc, pAcGal*Antp*Luc, pAcGal*Lab*Luc, pAcDsRedEGFP, pAcDsRed*LabEGFP,* pCycBGalLuc, pCycBGal*EMCV*Luc, pCycBGal*Lab*Luc, pAcGal*Ubx*Luc,pGal*N*Luc, pCMVGalLuc, pCMVGal*EMCV*Luc, pCMVGal*hBip*Luc, pCMVGal*A1*Luc, pAcLab(1-239), pAcLab(1-215), pAcLab(45-239), pAcLab(45-215), pAcLab(1-74_187-215), pAcLab(1-74_187-239), pAcLab(124-7 GGGG), A1(136-9AAAA), pAcEGFP*Lab*Hyg, pOpIE2GalLuc, pOpIE2Gal*EMCV*Luc,pOpIE2Gal*lab*Luc, and pOpIE2GalΔ*lab*Luc, pPolhLuc*EMCV*EGFP, pPolhLuc*lab*EGFP, and pPolhLuc*EMCV*GFP), the host cells containing these vectors (specifically stable cell lines, Drosophila S2 cells (Example 8)) containing these vectors, and recombinant baculovirus (Example 9, pages 41-43). Since the constructs, host cells containing them, and recombinant baculovirus are essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. Despite the fact that cloning DNA into vectors is well known in the art, there is no way of guaranteeing that a construct made by a skilled artisan will be exactly the same as the one used in the present Invention. Similarly, there is no way of guaranteeing that each stable Drosophila cell line or recombinant baculovirus taught in this specification will be exactly the same as that generated by another skilled artisan. If the cell lines are not so

obtainable or available, the requirements of 35 U.S.C. 112, regarding "how to make", may be satisfied by a deposit of cell lines. If the deposits are made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific cell lines have been deposited under the Budapest Treaty and that the cell lines will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement.

It the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will afforded to the Commissioner upon request;
(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;
(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request of for the effective life of the patent, whichever is longer; and,
(d) a test of viability of the biological material at the time of deposit (see 37 CFR 1.807); and,
(e) the deposit will be replaced if it should ever become inviable.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed

invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Claims 1-11, 17, 18 are broad because the claims broadly encompasses any promoter. However, even after the time of filing, one skilled in the art does not know how to reliably isolate any length of genomic DNA and know that it would function as a promoter. A skilled artisan would not necessarily know in what cell types the promoter would function. Claim 1 broadly encompasses any promoter. However, characterization of any promoter is a lengthy process. Goswami et al. (2003, Journal of Molecular Evolution, 57:44-51) teach some of the analyses used to characterize a promoter. Goswami et al. show by 5' deletion analysis that BD2, a greater 5' deletion of the TGF-β5 promoter than BD3, has more activity than BD3, suggesting that the 5' deletion in BD2 uncovered a negative regulator in the promoter (page 46, column 2, first paragraph, lines 3-7). Goswami et al. also show that while there is this difference in promoter activity between the two constructs transfected in XTC cells (*Xenopus* tadpole

cell line), there is no difference in the activity of the promoters when transfected in A6 cells (*Xenopus* adult kidney fibroblast cell line). This result suggests that there is a difference in the transcriptional factors between the cell types (page 46, column 2, first paragraph, lines 7-10). Goswami et al. also show that there is a difference in promoter regulation, depending what animal species that promoter is from and into which cells the reporter construct is transfected. TGF-β5, which is found in rats and frogs, was found to be regulated differently. *Xenopus* TGF-β5 transfected into *Xenopus* cells had activity; it had little to no activity when transfected into mammalian cells (page 47, column 2, section headed "Basal Promoter Activites of TGFβ1 and TGF-β5 Promoter in Mammalian Cell Lines", see also Figures 3 and 4).

As illustrated by Goswami et al., selecting a regulatory region of a gene as a promoter is not intuitive and requires extensive characterization. This is undue experimentation. One skilled in the art cannot define a regulatory region of a gene as a promoter and expect that another skilled in the art would select the same sequence without guidance.

Claims 6, 18, 23, 24, 25, 26, 27, 29, 30, 31, 33, 34, 35 broadly encompass any homolog of SEQ ID NO.1. However, at the time of filing, neither the art nor the specification teaches what characteristics a 5' untranslated region (UTR) would have to predictably function as an internal ribosome entry site (IRES). Rather, the art has shown that the identification of an IRES is done empirically. Furthermore, the specification teaches that while the *lab* gene is evolutionarily conserved in humans as the human Homeobox A1 and that the predicted folding of the Homeobox A1 5'UTR

was predicted to fold into a Y stem-loop structure similar to that of the *lab* 5' UTR, the Homeobox A1 5' UTR was tested for IRES activity. For this reason, one cannot assume that because the 5' UTR of labial and of Homeobox A1 function as an IRES that all other homologs of labial and Homeobox A1 function as an IRES. Rather, all other homologs' 5' UTR would need to be tested for IRES activity.

Claims 1-11, 17, 18, 20-22, 24, 25 are to a "variant" or "fragment" of SEQ ID NO. 1. However, the specification does not teach how to make a variant or fragment of SEQ ID NO. 1 such that it functions as an IRES. "Variant" is a broad term and in context of claims 1 and 6, it could mean a chemical variant or a variant having base changes. However, the specification does not teach how to make any chemical variants, nor does the specification teach how to add, remove, or substitute any number of nucleic acid bases such that the variant has IRES activity, beyond that which has been taught in the specification (page 38, Lab (124-7 GGGG) and Homeobox A1 (136-9 AAAA)). "Fragment" is a broad term and in context of claims 1 and 6, it could mean a fragment of one or two nucleic acids, or it could mean a fragment of fifty nucleic acids. However, the specification does not teach how to use these one-mer, two-mer, fifty-mers as an IRES. The specification has not taught how to make any fragments of SEQ ID NO. 1 that have IRES activity, beyond those disclosed in the specification (page 34, Table 2; page 41, Δlab of pOpEl2GalΔ*lab*Luc).

Claims 12-16 are to a host cell comprising a nucleic acid vector. Claim 12 is to a host cell comprising the nucleic acid vector of claim 1. Claim 15 is to a host cell

comprising the nucleic acid vector of claim 6. Claims 13 and 14 depend from claim 12 and claim 16 depends from claim 15. Claims 12 and 15 are broad for "host cell." This means that claim 12 can be read as a mammalian cell comprising the nucleic acid vector of claim 1 and that claim 15 can be read as a Drosophila cell comprising the nucleic acid vector of claim 6. However, it is not known in the art that CMV is a promoter that can be used to drive mRNA expression in Drosophila cells. The specification points out that the actin 5C distal promoter used in Drosophila does not function in mammalian cells (page 33, first paragraph). For these reasons, claim 12 does not enable one skilled in the art to make or use any host cell comprising a nucleic acid vector of claim 1; claim 15 does not enable one skilled in the art to make or use any host cell comprising a nucleic acid vector of claim 6.

In view of the quantity of experimentation necessary, the amount of direction or guidance presented, the absence of working examples, the nature of the invention, the state of the prior art, the unpredictability of the art, and the breadth of the claims, at the time the claimed invention was made, it would have required unde experimentation to make and/or use the invention as claimed.

Claims 1-6, 8-19, 20-27, 29-31, 33-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The final Written Description Examination guidelines that were published on January 5, 2001 (66 FR 1099; available at http://www.uspto.gov/web/menu/current.html#register).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

While the specification describes a pAC, pCMV, OpIE2, pCycB, polh promoter, the specification does not enable one to make and/or use any promoter. The specification also teaches SEQ ID NO. 1, SEQ ID NO. 2, pAcLab(1-239), pAcLab(1-215), pAcLab(45-239), pAcLab(45-215), pAcLab(1-74_187-215), pAcLab(1-74_187-239), pAcLab(124-7 GGGG), A1(136-9AAAA), and Δlab were functional IRESes, but the specification does not enable one to make and/or use any variant, fragment, or homolog of SEQ ID NO. 1. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the

invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, the specification teaches that pAC, pCMV, OpIE2, pCycB, polh promoters were used to drive expression of dicistronic mRNA. However, claims 1-19 are broad for all promoters. One skilled in the art cannot readily envision any length of DNA and readily identify it as a promoter. The specification does not teach what characteristics would qualify a length of DNA as a promoter. Further, the art teaches that a region of genomic DNA that is purported to be a promoter must then be tested to determine whether it is one. The art and the specification also teaches that certain promoters function in certain cell types. For example, as taught in the Goswami et al. example above, *Xenopus* TGF-β5 transfected into *Xenopus* cells had activity; it had little to no activity when transfected into mammalian cells (page 47, column 2, section headed "Basal Promoter Activites of TGFβ1 and TGF-β5 Promoter in Mammalian Cell Lines", see also Figures 3 and 4). The specification teaches that the actin 5C distal promoter functions in Drosophila cell, whereas it does not function in mammalian cells (page 33). Thus, the specification does not fulfill the written description requirement for all promoters. The specification also teaches that SEQ ID NO. 1, SEQ ID NO. 2, pAcLab(1-239), pAcLab(1-215), pAcLab(45-239), pAcLab(45-215), pAcLab(1-74_187-215), pAcLab(1-74_187-239), pAcLab(124-7 GGGG), A1(136-9AAAA), and Δlab function as IRESes. Claims 1-6, 8-18, 20-27, 29-31, 33-35 are broad for a homolog, variant or fragment of

SEQ ID NO. 1 which provide IRES activity. However, a skilled artisan cannot envision all homologs, variants, and fragments of SEQ ID NO. 1 which have IRES activity. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of identifying it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only pAC, pCMV, OpIE2, pCycB, polh meet the written description provision of 35 U.S.C. §112, first paragraph for promoters and SEQ ID NO. 1, SEQ ID NO. 2, pAcLab(1-239), pAcLab(1-215), pAcLab(45-239), pAcLab(45-215), pAcLab(1-74_187-215), pAcLab(1-74_187-239), pAcLab(124-7 GGGG), A1(136-9AAAA), and Δlab meet the written description provision of 35 U.S.C. §112, first paragraph for functional IRES. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicants attention is drawn to the decision of *The Regents of the University of California v. Eli Lilly and Company* (CAFC, July 1997) wherein it was stated:
In claims involving chemical materials, generic formulas usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a

formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate written description of the claimed genus. In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See *Fiers,* 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing *Amgen*). It is only a definition of a useful result rather than a definition of what it achieves as a result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. *See In re Wilder*, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

Because Applicants have failed to provide an adequate written description of the materials used in the compositions and methods claimed and because there is no evidence that Applicants possessed any promoter or IRES beyond that disclosed and/or known in the prior art, the rejected claims fail to meet the written description requirement under 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, Ph.D. can be reached on 571-272-0804. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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